

REMARKS

By the present communication, claims 1-32, 36-42 and 44-46 are pending and have been examined while claims 33-35 and 43 have been withdrawn. Applicant reserves the right to pursue all subject matter excluded by the present amendments in future continuation or divisional applications. Claim 46 has been added to correct dependency of claim 32. Claims 1, 3, 4, 6, 8, 12, 13, 15, 19-22, 24, 26-28, 32, 36, 38, 39, 41, and 44-45 have been amended to correct typographical errors and further clarify antecedent basis. Thus, the amendments do not raise any issue of new matter.

Applicant respectfully requests reconsideration of the present application in view of the foregoing amendments and in view of the reasons which follow.

Information Disclosure Statement

Applicant respectfully disagrees with the Examiner's assertion that the English abstract provided for the foreign patent submitted as document A5 in the IDS filed January 22, 2004 fails to comply with 37 CFR 1.98(a)(3). Applicant acknowledges that a concise explanation must be provided for a reference that is not in English, however, a "[s]ubmission of an English language abstract of a reference may fulfill the requirement for a concise explanation." MPEP 609.04(a)(III). The Examiner has acknowledged having and considering such an abstract for document A5. Office Action, p. 4. lines 10-11.

In any event, Applicant has found, and provided herewith in an IDS, the English-language equivalent of A5, U.S. Patent No. 6,660,478, which also fulfills the compliance requirement for foreign applications. MPEP 609.04(a)(III). As such, Applicant submits that the previous IDS complies with 37 CFR 1.98(a)(3) both by its inclusion of an English abstract and/or by provision of an English counterpart application, provided herewith.

Objections to Claims

The Examiner's objections to claims 32 and 45 are acknowledged. In view of the amendments to claims 32 and 45, Applicant respectfully requests reconsideration and withdrawal of the objections.

Specification

The specification has been amended to correct references to trademarks in the description of the invention as noted by the Examiner. Accordingly, withdrawal of the various objections is respectfully requested.

Rejection of claims 1-32, 36-42 and 44-45 under 35 U.S.C. § 112, Second Paragraph, Indefiniteness

The rejections of claims 1-32, 36-42 and 44-45 under 35 U.S.C. § 112, first paragraph, as allegedly lacking written description, is respectfully traversed. The Examiner's effort to improve the claims is acknowledged with appreciation. Applicants have carefully considered each rejection and provide a suitable amendment to obviate the issue. Accordingly, withdrawal of the rejection is respectfully requested.

Applicants respectfully traverse the rejection as to the term "relating." The Examiner contends that "it is not clear what is encompassed by the term relating and how this step relates to the act of identifying." Office Action, page 6. In support, the Examiner asserts that it is unclear if relating "requires identification of 'one of a plurality of preselected polymorphisms' or does it merely require 'relating' a labeled nucleic acid to a polymorphism?"

As amended, the relating step reads as follows:

b) relating the at least one labeled nucleic acid to the identity of at least one of said preselected polymorphisms in said sample.

Applicants respectfully submit that the “relating step” is clear and simply requires that identity of each polymorphism present in the sample be deduced from the labeled nucleic acids produced by primer extension. The method of labeled single nucleotide primer extension is well known in the art and is used to relate an extension product with a particular base sequence. Relating each primer extension product to the identity of each polymorphism that produced it can be done, for example, by size separation electrophoresis. In this regard, the specification describes separating the labeled extension products by electrophoresis (see [0036]) and separating according to size (see [0109]). Further table 3 provides various length primers designed to relate the size of the product to the identify of the particular polymorphism. One of ordinary skill would understand that the labeled extension products need to be related to the identify of the individual polymorphisms. Accordingly, Applicants submit that the “relating” language is clear and definite within the meaning of Section 112, Second Paragraph.

Nevertheless, to assist in better understanding by the Examiner, Applicants have replaced the relating clause with a requirement to use the labeled nucleic acids produced by primer extension to identify the preselected P450 2D6 polymorphisms present in a nucleic acid sample.

**Rejections of claims 1-2, 4, 6-9, 11-20, 22, 24-27 and 29-32 under 35 U.S.C. § 102 by
Anastasio in light of Goelet**

The rejections of claims 1-2, 4, 6-9, 11-20, 22, 24-27 and 29-32 under 35 U.S.C. § 102(a) and (e) as being anticipated by Anastasio et al (WO02/38589; hereinafter “Anastasio”) in light of Goelet et al. (WO92/15712; hereinafter “Goelet”), are respectfully traversed.

In order to anticipate a claim, a single prior art reference must provide each and every element set forth in the claim. Furthermore, the claims must be interpreted in light of the teaching of the specification. *In re Bond*, 15 USPQ2d 1566, 1567 (Fed. Cir. 1990). *See also* MPEP § 2131. The Examiner bears the initial burden of establishing a *prima facie* case of anticipation. Only once that *prima facie* case has been established does the burden shift to the applicant to rebut the *prima facie* case. *See, e.g., In re Morris*, 127 F.3d 1048, 1054 (Fed. Cir. 1997).

Claim 1 and dependent claims require identifying at least one cytochrome P450 2D6 polymorphism in a single nucleotide extension format performed using a plurality of extension primers each for a different cytochrome P450 2D6 polymorphism and a distinctively labeled set of ddNTPs. The production of labeled extension primers is then used to identify the cytochrome P450 2D6 polymorphisms present in the sample. Claim 19 is similar to claim 1 but has the additional requirement for the extension primers for each polymorphism to differ in length and subjecting the labeled extension primers to a size separation method.

Anastasio discloses polymerase mediated primer extension reactions for detecting polymorphisms in cytochrome P450 2D6. Anastasio describes a primer extension oligonucleotide with the 3' end located immediately adjacent to the polymorphic site yet refers to the primer as being "downstream" of the polymorphic site. See page 18. Goelet describes single nucleotide primer extension with distinctively labeled ddNTPs. Neither Anastasio or Goelet describe a single reaction for P450 2D6 polymorphism detection that uses multiple extension primers and distinctively labeled ddNTPs.

Anastasio in view of Goelet is even more deficient respect to claim 19 and its dependent claims in failing to disclose a single reaction for P450 2D6 polymorphism detection that uses multiple extension primers, wherein the primer for each polymorphism differs in length, and further includes distinctively labeled ddNTPs.

Thus, Applicant respectfully submits that Anastasio in view of Goelet fails to disclose each and every limitation of the claimed invention. Reconsideration and withdrawal of the rejection is respectfully requested.

Rejection of claims 5 and 23 under 35 U.S.C. § 103(a)

The rejection of claims 5 and 23 under 35 U.S.C. § 103(a) as allegedly being obvious over Anastasio in view of Dovichi and Zhang, 167 Methods in Molecular Biology 225-239 (2001; "Dovichi"), in light of the teachings of Goelet, is respectfully traversed.

In order to establish a *prima facie* case of obviousness, it is necessary that the prior art disclose each and every limitation of the claim, that there is a reasonable expectation of success,

and that there is some motivation, either in the prior art references or in the knowledge of a person of ordinary skill in the art, to make the asserted combination or modify or combine the reference teachings. *KSR International Co. v. Teleflex Inc.*, ___ U.S. ___ (2007); *In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991); MPEP § 2143.

As described above, Anastasio alone or in light of Goelet fails to disclose a single reaction for P450 2D6 polymorphism detection that uses multiple extension primers and distinctively labeled ddNTPs.

Dovich and Zhang are unable to cure the deficiencies of Anastasio in light of Goelet. Dovich and Zhang generally disclose DNA sequencing by capillary array electrophoresis. In fact, none of the methods in Dovich are directed to P450 2D6 or single nucleotide extension. Accordingly, none of Anastasio in light of Goelet or Dovich/Zhang alone or in any combination describe a single reaction for P450 2D6 polymorphism detection that uses multiple extension primers and distinctively labeled ddNTPs.

Thus, because the cited references alone or in combination fail to provide a *prima facie* case of obviousness, Applicant respectfully requests reconsideration and withdrawal of the rejection.

Rejection of claims 10, 28, 36-37, 39 and 41-42 under 35 U.S.C. § 103(a)

The rejection of claims 10, 28, 36-37, 39 and 41-42 under 35 U.S.C. § 103(a) as allegedly being obvious over Anastasio in view of Pastinen et al, PCR Applications, p. 521-535 (1999; “Pastinen”), in light of the teachings of Goelet, is respectfully traversed.

The instant claims require identifying one of a plurality of cytochrome P450 2D6 polymorphisms by using a plurality of extension primers for single nucleotide extension with distinctively labeled ddNTPs and using the resulting labeled nucleic acid to identify a polymorphism. In addition, claims 10, 28, 36-37, 39 and 41-42 further require that the polymorphisms be selected from a list, for example as in claim 9, and further require that the extension primer sequences be one of SEQ ID NOs: 9-19.

As described above, Anastasio in light of Goelet fails to disclose a single reaction for P450 2D6 polymorphism detection that uses multiple extension primers and distinctively labeled ddNTPs.

Pastinen is unable to cure the deficiencies of Anastasio in view of Goelet. Pastinen discloses detecting P450 2D6 polymorphisms using a solid-phase support in combination with separate primer extension reactions for each ddNTP. Nowhere does Pastinen teach to use a single reaction with multiple extension primers with distinctively labeled ddNTPs. Moreover, Pastinen teaches away from using distinctively labeled ddNTPs (i.e., four different fluorophores) by stating that multiple labels would not increase capacity compared to Pastinen's disclosed method. *See* PCR Applications, p. 532, lines 24-31. Thus, one of skill in the art would not be motivated to alter the Pastinen method to arrive at the instantly claimed invention.

Furthermore, the Examiner asserts that it would be obvious to use Pastinen's CYP2D6*4 allele primer to arrive at SEQ ID NO:9 of the instant claims, which differ by four bases. However, one of skill in the art would not be motivated by the Pastinen reference to alter the oligonucleotide as such because Pastinen states "[p]rimers differing in size by one or two bases could be used if required." As such, one of skill in the art reading the Pastinen reference would not be motivated to alter the primer by more than two bases.

Therefore, the combination of references fails to disclose each and every element of independent claim 1, from which all claims under this rejection depend in addition to the additional limitations of claims 10, 28, 36-37, 39 and 41-42. Because the cited references alone or in combination fail to provide a *prima facie* case of obviousness, Applicant respectfully requests reconsideration and withdrawal of the rejection.

Rejection of claim 40 under 35 U.S.C. § 103(a)

The rejection of claim 40 under 35 U.S.C. § 103(a) as allegedly being obvious over Anastasio in view of Pastinen, in light of the teachings of Goelet as applied to claims 10, 28, 36-37, 39 and 41-42, and further in view of Dovichi, is respectfully traversed.

Claim 40 requires identifying one of a plurality of cytochrome P450 2D6 polymorphisms by using a plurality of extension primers for single nucleotide extension with distinctively labeled ddNTPs and relating the resulting labeled nucleic acid to a polymorphism, using at least one extension primer having SEQ ID NOs: 9-19, and mobilizing the labeled nucleic acid by capillary electrophoresis.

As described above, the combination of Anastasio, Pastinen and Goelet fails to establish a *prima facie* case of obviousness. Dovichi is unable to cure the deficiencies of the cited references because Dovichi generally discloses DNA sequencing by capillary array electrophoresis. Moreover, none of the methods in Dovichi are directed to P450 2D6 or single nucleotide extension.

Thus, because the cited references alone or in combination fail to provide a *prima facie* case of obviousness, Applicant respectfully requests reconsideration and withdrawal of the rejection.

Conclusion

In view of the above amendments and remarks, reconsideration and favorable action on all claims are respectfully requested. In the event any matters remain to be resolved in view of this communication, the Examiner is encouraged to contact the undersigned so that a prompt disposition of this application can be achieved.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16 1.17, or credit any overpayment, to Deposit Account No. 50-0872. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 50-0872. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 50-0872.

Respectfully submitted,

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